

REMARKS

The remainder of this Amendment is set forth under appropriate subheadings for the convenience of the Examiner.

Status of the Claims

Claims 1-97 are pending in the instant application. Claims 1, 24, 47 and 66 are withdrawn from consideration, and Claims 2-23, 25-46 48-65 and 67-97 are rejected.

Amendments to the Claims

Claims 2, 25 and 67 have been amended to recite the step of contacting a β -cyanoethyl protected oligonucleotide or oligonucleotide analog with an aqueous basic solution comprising at least one substituted or unsubstituted sterically hindered primary aliphatic amine. Support for this amendment can be found in original Claims 2, 25 and 67 themselves and original Claims 10, 33 and 72. Claim 67 has been further amended to recite that in the claimed method, modification of the oligonucleotide or oligonucleotide analog is substantially prevented during removal of "at least one" β -cyanoethyl protecting group. Support for this amendment can be found in Claim 67 itself, as originally filed. Additional support for this amendment can be found, for example, in Claims 2 and 25.

Claim 9 has been amended for consistency of language.

Claims 10, 12, 33, 35, 56, 72, 77 and 79 have been amended to be consistent with Claims 2, 25 and 67, as currently amended. Claims 10, 12, 33, 35, 56, 77 and 79 have been further amended to correct dependency, and now depend from Claims 8, 2, 31, 25, 54, 75 and 67, respectively.

Self-obvious various typographical errors have been amended in Claims 2, 20, 21, 22, 29, 30, 43, 44, 45, 62, 63, 64, 86, 93, 94, 95 and 97.

Claims 3, 4, 5, 11, 26, 27, 28, 34, 49, 50, 51, 68, 69, 70 and 78 are canceled. Dependency of Claim 97 has been amended to be consistent with the cancellation of these claims.

Rejection of Claims 49-51 under 35 U.S.C. § 112, second paragraph

Claims 49-51 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 49-51 have been canceled, obviating this rejection.

Rejection of Claims 2-6, 8-10, 14, 15, 18-22, 25-28, 31-33, 37-45, 48-52, 54-64, 67-72, 75-79, 81, 82 and 85-97 under 35 U.S.C. § 102(b)A. Summary of the Rejection

Claims 2-6, 8-10, 14, 15, 18-22, 25-28, 31-33, 37-45, 48-52, 54-64, 67-72, 75-79, 81, 82 and 85-97 are rejected under 35 U.S.C. § 102(b) as being anticipated by Sinha, *et al.*, *Nucleic Acids Research*, 12: 4539-4557 (1984) (hereinafter "Sinha, *et al.* ") In particular, the Examiner stated that Sinha, *et al.* disclose the use of a *t*-BuNH₂/pyridine mixture for the removal of a β-cyanoethyl group prior to contacting with an aqueous ammonia solution. The Examiner also stated that when the aqueous ammonia solution is added to the *t*-BuNH₂/pyridine mixture, this forms an aqueous basic solution comprising an acrylonitrile scavenger (e.g., *t*-BuNH₂), and therefore anticipates the listed claims of the present application. Applicant respectfully submits that the Examiner is incorrect in this matter for the reasons set forth below.

B. Applicant's Invention

Applicant's invention of independent Claims 2, 25 and 67, as currently amended, and independent Claim 48 is directed to methods for preventing modification of β-cyanoethyl protected oligonucleotides or oligonucleotide analogs during the de-β-cyanoethylation process of the oligonucleotides. In particular, the methods of independent Claims 2, 25 and 67, as currently amended, require contacting a β-cyanoethyl protected oligonucleotide or oligonucleotide analog with an aqueous, basic solution comprising at least one substituted or unsubstituted sterically hindered primary aliphatic amine. The method of Claim 48 requires contacting a β-cyanoethyl protected oligonucleotide or oligonucleotide analog with an ammonium hydroxide solution (an

aqueous basic solution) comprising *tert*-butylamine (a sterically hindered primary aliphatic amine acrylonitrile scavenger). Notwithstanding the other features specified, each of these claims therefore requires the use of ***both*** of an aqueous, basic solution ***and*** a sterically hindered primary aliphatic amine acrylonitrile scavenger.

C. Applicant's Invention Is Novel in view of Sinha, *et al.*

Sinha, *et al.* disclose processes for the de- β -cyanoethylation of an oligonucleotide. These are described on page 4546, and fall into two distinct categories. The first is a stepwise process wherein β -cyanoethyl groups are removed by a solution of either *tert*-butylamine or triethylamine in pyridine (a ***non-aqueous*** solution), followed by cleavage from the solid support using aqueous ammonia. The second is a single step process wherein β -cyanoethyl groups are removed and cleavage from the solid support achieved by treatment ***solely with aqueous ammonia***.

There is no disclosure or suggestion in Sinha, *et al.* of a method requiring the use of ***both*** of an aqueous, basic solution ***and*** an acrylonitrile scavenger. In particular, with respect to the Examiner's assertion summarized above, there is no teaching in Sinha, *et al.* that the ammonia solution is added to the *tert*-butylamine/pyridine solution. Sinha, *et al.* simply disclose that the ammonia treatment follows the *tert*-butylamine treatment.

Moreover, even if the ammonia solution is added to the *tert*-butylamine/pyridine solution (and this is not admitted in Sinha, *et al.*), this combined solution is ***not*** employed to remove β -cyanoethyl groups. The clear teaching of the third full paragraph on page 4546 is that the β -cyanoethyl groups are removed by the *tert*-butylamine/pyridine solution ***prior to*** the cleavage from a polymeric solid support and removal of acyl base protecting groups by ammonia (emphasis added):

The deprotection, in our synthetic strategy with the β -cyanoethyl group as phosphate protection, may be achieved: either by stepwise deprotections, where *t*-BuNH₂/Pyridine (or Et₃N/Pyridine) mixture is used for the ***removal of β -cyanoethyl group, followed by N-deacylation and cleavage from the polymer with conc. aq. NH₃***, or one step deprotections by conc. aq. NH₃ ***alone***.

As clearly stated above, the whole point of the two-stage deprotection process taught by Sinha, *et al.* is that the betacyanoethyl groups are removed by *tert*-butylamine/pyridine solution before the use of ammonia. Sinha, *et al.* therefore do not disclose the use of an aqueous basic solution comprising an acrylonitrile scavenger for the removal of betacyanoethyl groups.

C. Summation

As discussed above, the subject matter of independent Claims 2, 25 and 67, as currently amended, and independent Claim 48 is novel in view of Sinha, *et al.*, because Sinha, *et al.* do not disclose or suggest a method requiring the use of **both** of an aqueous, basic solution **and** an acrylonitrile scavenger. Claims 3-6, 8-10, 14, 15, 18-22, 26-28, 31-33, 37-45, 48-52, 54-64, 68-72, 75-79, 81, 82 and 85-97 are dependent from independent Claims 2, 25, 48 and 67, respectively, and thus these claims are also novel in view of Sinha, *et al.* Applicant respectfully requests reconsideration and withdrawal of this rejection.

Rejection of Claims 2-5, 7-23, 25-46 and 67-97 under 35 U.S.C. § 102(e)

Claims 2-5, 7-23, 25-46 and 67-97 under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 6,465,628 Ba to Ravikumar, *et al.* (hereinafter "Ravikumar, *et al.*")

As discussed above, Applicant's invention of independent Claims 2, 25 and 67, as currently amended, employ an aqueous, basic solution comprising at least one substituted or unsubstituted **sterically hindered** primary aliphatic amine.

Ravikumar, *et al.* disclose certain amines which can be employed in the deprotection of oligonucleotides (see Example 22). However, none of these amines are sterically hindered primary aliphatic amines. Further, the amines disclosed in Example 22 of Ravikumar, *et al.* are not taught to be acrylonitrile scavengers, and indeed these amines are excluded from the list of scavengers disclosed at, for example, col 5, lines 31-57. The only aliphatic amine included in the extensive list of possible scavengers disclosed by Ravikumar, *et al.* is linear n-butylamine, which is **not** a sterically hindered amine. At no point does Ravikumar, *et al.* disclose, or suggest, the use of an aqueous, basic solution comprising a sterically hindered primary aliphatic amine.

Therefore, Ravikumar, *et al.* do not disclose each and every feature of independent Claims 2, 25 and 67, as currently amended, and therefore does not anticipate these claims. For

the same reasons, the subject matter of Claims 3-5, 7-23, 26-46 and 68-97, which are dependent from independent Claims 2, 25 and 67, respectively, is also novel in view of Ravikumar *et al.* Accordingly, Applicant respectfully requests reconsideration and withdrawal of this rejection.

Rejection of Claims 53 and 65 under 35 U.S.C. § 103(a)

Claims 53 and 65 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Sinha, *et al.* in view of Ravikumar, *et al.*

Claims 53 and 65 depend from independent Claim 48, and are directed to the method of Claim 48, employing an ammonium hydroxide solution (an aqueous basic solution) comprising *tert*-butylamine (a sterically hindered primary aliphatic amine acrylonitrile scavenger).

As discussed above, Sinha, *et al.* do not teach a deprotection process employing both of an aqueous, basic solution and an acrylonitrile scavenger, e.g., *tert*-butylamine. Also, Sinha, *et al.* expressly disclose that it is preferred to employ an aqueous solution comprising only ammonia in order to achieve deprotection and cleavage in a single step (see, for example, conclusion 5, p4552). The *tert*-butylamine is disclosed only for use in solution in pyridine (a non-aqueous solution) in the less preferred two-step deprotection and cleavage process. Moreover, there is no suggestion in Sinha, *et al.* that *tert*-butylamine would have any acrylonitrile scavenging properties. Accordingly, there is nothing in Sinha, *et al.* that would motivate one of ordinary skill to employ an aqueous, basic solution comprising at least one substituted or unsubstituted sterically hindered primary aliphatic amine for removing β -cyanoethyl groups.

Ravikumar, *et al.* make no mention of the use of sterically hindered primary aliphatic amines as acrylonitrile scavengers. The only primary aliphatic amine contemplated by Ravikumar, *et al.* as a acrylonitrile scavenger is a ***non-hindered*** *n*-butylamine which is structurally distinct from the sterically hindered *tert*-butylamine of Sinha, *et al.* There is no suggestion or teaching in Ravikumar, *et al.* that would lead one of ordinary skill to select a new class of scavengers, i.e., sterically hindered primary aliphatic amines on which Ravikumar, *et al.* are completely silent.

Accordingly, it is submitted that the subject matter of Claims 53 and 65 would not have been obvious to one of ordinary skill in the art in view of Sinha, *et al.* and Ravikumar, *et al.*, taken either separately or in combination. Reconsideration and withdrawal of this rejection are respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all pending claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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